National Center for Computational Sciences Snapshot The Week of March 24, 2008

<u>Potassium Channel Model Lights the Way for Simulations of Molecular Machines</u>
Supercomputers to reveal in atomistic detail all steps from open to closed ion channel

Scientists are using resources at the National Center for Computational Sciences (NCCS) to simulate in unprecedented detail the voltage-gated potassium channel, a membrane protein that responds to spikes of electricity by changing shape to allow potassium ions to enter a cell. “The study will serve as a future road map for simulating, visualizing, and elucidating the workings of molecular nanomachines,” says Professor Benoît Roux of Argonne National Laboratory and the University of Chicago.

In essence, a voltage-activated ion channel is a nanoscale device acting as an electric switch, he says. With University of Illinois at Urbana-Champaign researchers Klaus Schulten and Emad Tajkhorshid, Roux uses the leadership computing facility at Oak Ridge National Laboratory (ORNL) to model the channel in its open and closed states and determine the gating charge driving the change in conformation between the two states.

If the switch operates normally, the potassium channel opens when activated and closes when resting. But if gating malfunctions—and it can go awry in various ways—cardiovascular or neurological disease can result. The important functions of potassium channels in excitable cells make them good drug targets.

Roux’s team is using a computer program called Rosetta to predict the three-dimensional structure of the potassium-channel protein. For a given sequence of amino acids, Rosetta conducts a large-scale search for three-dimensional protein conformations that are especially low in free energy and assumes the native state is the one with the least free energy. The group found that simulations of the open and closed states are stable. Assessing stability is critical to supporting the model’s validity.

In a step toward achieving their long-term goal of understanding how membrane-associated molecular protein machines function, the researchers simulated the motion of all atoms in the system using a molecular dynamics code for parallel processing that was developed in Schulten’s lab. The code, called NAMD, uses Newton’s laws and an energy function to simulate protein behavior in steps on the order of one femtosecond, or trillionth of a second. By looking at how the potassium channel moves in tiny, ultrafast increments, researchers can build a biologically meaningful picture of its dynamics.

Roux’s group received funding from the National Institutes of Health and an allocation of NCCS supercomputer time through a Department of Energy program called INCITE (for Innovative and Novel Computational Impact on Theory and Experiment). In 2007 the researchers used about 2.5 million processor hours on the NCCS’s Cray XT Jaguar supercomputer to model the behavior of systems with up to 350,000 atoms. “We are in the process of unraveling the atomistic basis for the coupling between a voltage-gated channel and the transmembrane electric potential," says Roux, whose group has received a 2008 INCITE grant of 3.5 million hours on Jaguar to continue the studies.

ORNL Offers Supercomputing Time to Universities

Laboratory to open supercomputing facilities to students, faculty

ORNL will grant access to its supercomputing systems to university students and faculty through a collaborative program with Oak Ridge Associated Universities (ORAU).

Two grants will be awarded each year, with each team receiving $75,000 for 3 years. The laboratory will make available its leading computer systems, relevant staff, and possibly other necessary resources to those teams that receive grants, helping them perform the best research possible. "We all become stronger if we can bring the best of what the lab has to offer coupled with the best of what the university community has to offer," said Thomas Zacharia, associate laboratory director for ORNL's Computing and Computational Sciences Directorate. "And we have a tremendous partner in ORAU that engages graduate, undergraduate, postdoctoral students, and faculty in scientific discovery through advanced computing."

NCCS Alters HPSS Storage System

New system dubbed Site-Style

The NCCS has modified the accounting system to its High Performance Storage System (HPSS). The new system, known as Site-Style, is a more project-specific data management system, said Vicky White, who led the transition. While each user will still have a default account similar to that used in the past system, the user can now assign files to any specific project that he or she is working on. The user, said White, has a number of project codes for which he or she is authorized, thereby providing the ability to separate data by the project to which it belongs. This way the user can easily find which files are associated with which projects. And, said NCCS staff member Mitch Griffith, "the principal investigators can actually monitor what users are storing, such as the number of files and the amount of data."

Furthermore, as usage of HPSS space increases over time, this new accounting style will enable the NCCS to better determine which projects need additional space. In addition to White and Griffith, the site-style accounting transition team consisted of NCCS staff members Chris Fuson, Jason Hill, and Bill Renaud.

MADNESS Opens the Door to Parallel Worlds

Programming environment to simplify computing

Veteran INCITE researcher Robert Harrison recently participated in the NCCS's Seminar Series to discuss MADNESS (Multiresolution ADaptive Numerical Environment for Scientific Simulation), a novel programming framework that could potentially benefit researchers in a number of areas.

Harrison, a computational chemist with ORNL, outlined the various levels of MADNESS, the lowest of which is a programming environment that makes it easy to write parallel programs without worrying about the more technical aspects of parallel computing. This tool, said Harrison, “takes over much of the responsibility of scheduling and even placement of computation.” The second level, said Harrison, “provides fast numerical computation in many dimensions with guaranteed precision. It provides a very high-level programming interface (in terms of physical functions and operators) while striving to express essentially all available parallelism.” Finally, Harrison discussed emerging applications in chemistry, molecular physics, and nuclear physics that are built within the framework.

The NCCS seminar series brings speakers to ORNL to share their research and expertise and to interact with NCCS staff. It also provides an opportunity for collaboration building and helps to communicate NCCS objectives and accomplishments throughout ORNL.